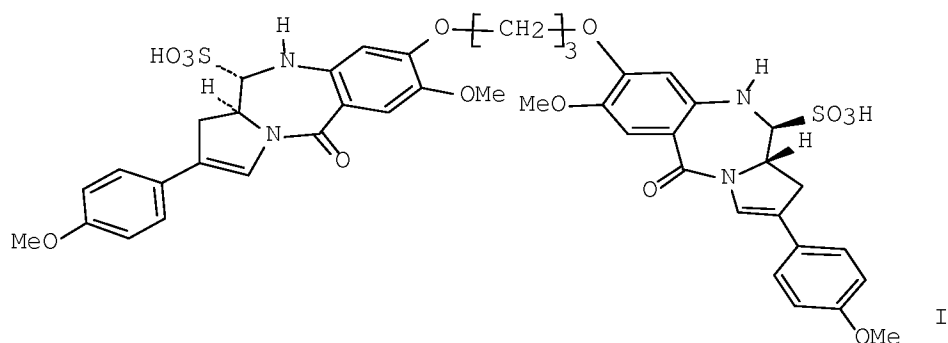


L5 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2009:1316122 CAPLUS Full-text  
 DN 152:74989  
 TI Synthesis of a novel C2/C2'-aryl-substituted  
 pyrrolo[2,1-c][1,4]benzodiazepine dimer prodrug with improved water  
 solubility and reduced DNA reaction rate  
 AU Howard, Philip W.; Chen, Zhizhi; Gregson, Stephen J.; Masterson, Luke A.;  
 Tiberghien, Arnaud C.; Cooper, Nectaroula; Fang, Min; Coffils, Marissa J.;  
 Klee, Sarah; Hartley, John A.; Thurston, David E.  
 CS The School of Pharmacy, Spirogen Ltd, London, WC1N 1AX, UK  
 SO Bioorganic & Medicinal Chemistry Letters (2009), 19(22), 6463-6466  
 CODEN: BMCLE8; ISSN: 0960-894X  
 PB Elsevier B.V.  
 DT Journal  
 LA English  
 GI



AB A prodrug form I·Na of a novel C2/C2'-aryl-substituted pyrrolobenzodiazepine (PBD) dimer II has been synthesized by introducing sodium bisulfite groups to the C11/C11'-positions of the parent bis-imine. The prodrug form is highly water soluble, stable in aqueous conditions, and the rate of DNA cross-link formation is much slower compared to the parent bis-imine.

IT 864754-68-7P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

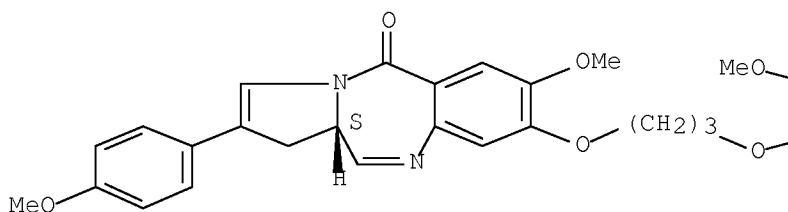
(preparation and antitumor activity of aryl-substituted pyrrolobenzodiazepine dimer via cyclization, triflation and Suzuki coupling of nitrobenzoic acid dimer with methoxyphenylboronic acid followed by formation of the bisulfite adduct)

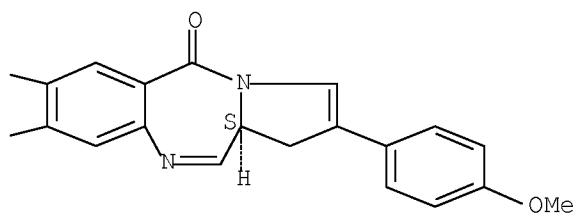
RN 864754-68-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one,  
 8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A





RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2006:1124678 CAPLUS Full-text  
 DN 145:455035  
 TI Preparation of pyrrolobenzodiazepine derivatives for treatment of  
 proliferative diseases  
 IN Gregson, Stephen John; Howard, Philip Wilson; Chen, Zhizhi  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 77pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2006111759	A1	20061026	WO 2006-GB1456	20060421
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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	AU 2006238686	A1	20061026	AU 2006-238686	20060421
	CA 2604805	A1	20061026	CA 2006-2604805	20060421
	GB 2439881	A	20080109	GB 2007-20721	20060421
	GB 2439881	B	20090408		
	EP 1879901	A1	20080123	EP 2006-726846	20060421
	EP 1879901	B1	20091223		
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	JP 2008536905	T	20080911	JP 2008-507165	20060421
	NZ 563136	A	20091127	NZ 2006-563136	20060421
	AT 452898	T	20100115	AT 2006-726846	20060421
	IN 2007DN07862	A	20071109	IN 2007-DN7862	20071011
	US 20080167293	A1	20080710	US 2007-911890	20071018
	US 7612062	B2	20091103		
	MX 2007013039	A	20080313	MX 2007-13039	20071019
	CN 101171257	A	20080430	CN 2006-80015716	20071108
	ZA 2007009615	A	20081126	ZA 2007-9615	20071108
	KR 2008004618	A	20080109	KR 2007-727047	20071120
PRAI	GB 2005-8084	A	20050421		
	GB 2005-22746	A	20051107		
	WO 2006-GB1456	W	20060421		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASREACT 145:455035; MARPAT 145:455035

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The title compds. with general formula I [wherein: R2 = (un)substituted aryl; R6 and R9 = independently H, R, OH, OR, SH, SR, NH2, NHR, NRR', nitro, Me3Sn, or halo, where R and R' = independently (un)substituted alkyl, heterocyclyl,

or aryl; R7 = H, R, OH, OR, SH, SR, NH2, NHR, NHRR', nitro, Me3Sn, or halo; Z = alkylene; X = O, S, or NH; n = 2 or 3] or pharmaceutically acceptable salts or solvates thereof are prepared for the treatment of proliferative diseases. For example, compound II•2Na was prepared in a multi-step synthesis. II•2Na showed IC50 of 1.5 nM in the In Vitro cytotoxicity test with K562 human chronic myeloid leukemia cells.

IT 913262-25-6P

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

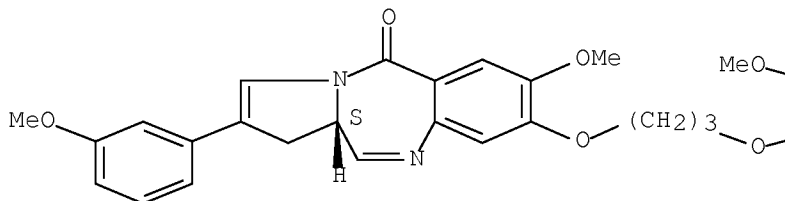
(preparation of pyrrolobenzodiazepine derivs. for treatment of proliferative diseases)

RN 913262-25-6 CAPLUS

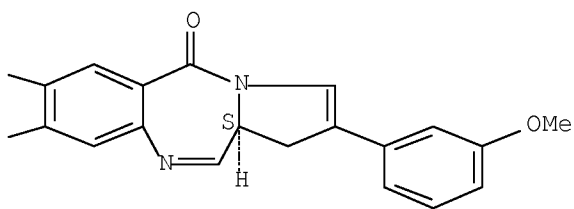
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one,  
8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(3-methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT 864754-68-7P 913262-40-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

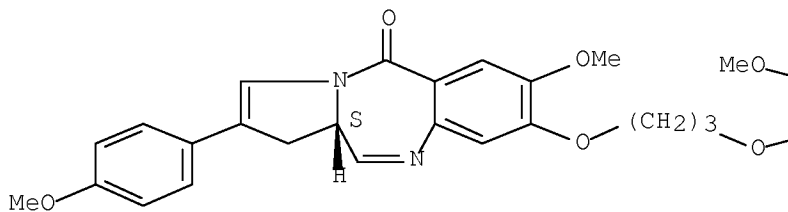
(preparation of pyrrolobenzodiazepine derivs. for treatment of proliferative diseases)

RN 864754-68-7 CAPLUS

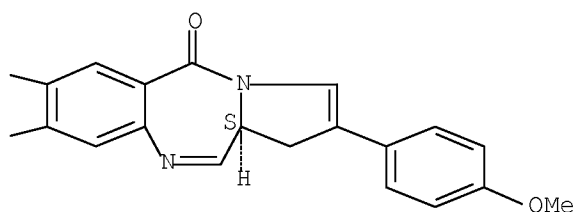
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one,  
8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



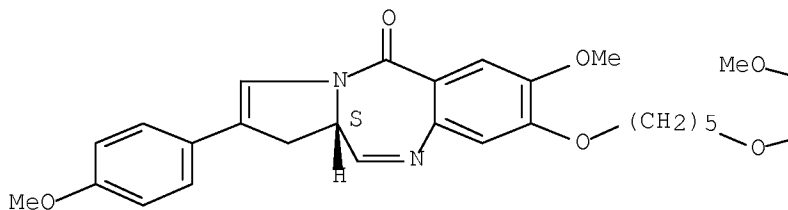
PAGE 1-B



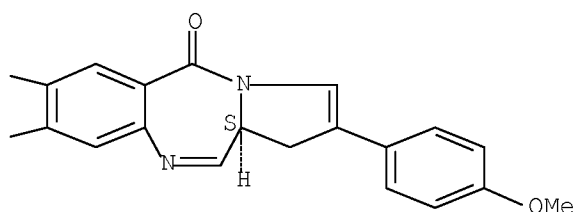
RN 913262-40-5 CAPLUS  
 CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one,  
 8,8'-[1,5-pentanediy]bis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-  
 methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2010 ACS on STN  
 AN 2005:1004748 CAPLUS Full-text  
 DN 143:306348  
 TI Preparation of pyrrolobenzodiazepinone derivatives as antitumor agents  
 IN Howard, Philip Wilson; Gregson, Stephen John  
 PA Spirogen Limited, UK  
 SO PCT Int. Appl., 88 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005085251	A1	20050915	WO 2005-GB768	20050301
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	AU 2005219626	A1	20050915	AU 2005-219626	20050301
	CA 2558195	A1	20050915	CA 2005-2558195	20050301
	EP 1720881	A1	20061115	EP 2005-717846	20050301
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	JP 2007525535	T	20070906	JP 2007-501340	20050301
	US 20070173497	A1	20070726	US 2007-598518	20070206
PRAI	GB 2004-4575	A	20040301		
	GB 2004-26392	A	20041201		
	WO 2005-GB768	W	20050301		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OS CASREACT 143:306348; MARPAT 143:306348

GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Title compds. I [R1 = labile leaving group, alkenyl or substituted phenyl; R2 and R5 independently = H, OH, SH, etc.; R3 and R4 independently = H, NH2, halo, etc. or the compound is a dimer with each monomer being of formula I, where the R3 and R4 groups of each monomer form together a dimer bridge -X-R-X-; R = alkylene group, which may be interrupted by heteroatoms or aromatic rings; X = O, S or NH; R6 = carbamate-based N-protecting group; R7 = oxygen protecting group or OH or R6 and R7 together form double bond between N10 and C11] and their pharmaceutically acceptable salts, are prepared and disclosed as antitumor agents. Thus, e.g., II was prepared by palladium catalyzed coupling of III (preparation given) with trans-propenylboronic acid followed by deprotection. The in vitro cytotoxicity of I towards K562 human chronic myeloid leukemia cells was evaluated using ELISA assay and it was revealed that selected compds. of the invention displayed IC50 values of less than 1  $\mu$ M. I should prove useful in the treatment of proliferative diseases such as leukemia. Pharmaceutical compns. comprising I are disclosed.

IT 864754-68-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

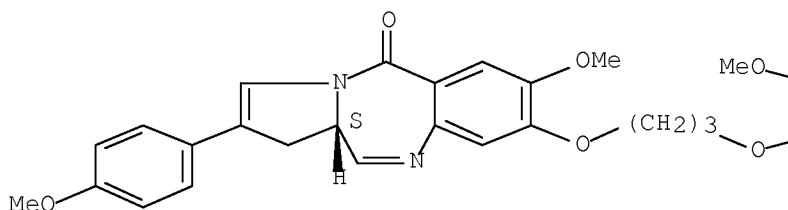
(preparation of pyrrolobenzodiazepinone derivs. as antitumor agents)

RN 864754-68-7 CAPLUS

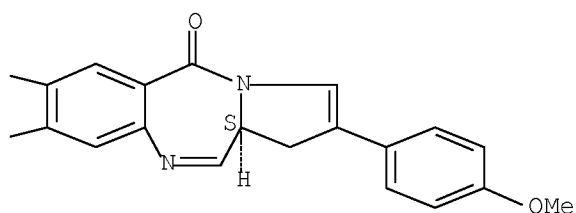
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one,  
8,8'-[1,3-propanediylbis(oxy)]bis[1,11a-dihydro-7-methoxy-2-(4-methoxyphenyl)-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B



RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L3               1 S L2  
L4               3 S L2 FUL

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\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

Structure attributes must be viewed using STN Express query preparation.

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FILE 'REGISTRY' ENTERED AT 16:23:53 ON 05 FEB 2010

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L3               1 S L2  
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FILE 'CAPLUS' ENTERED AT 16:24:28 ON 05 FEB 2010

L5               3 S L4

=> d l2; d his; log y

L2 HAS NO ANSWERS

L1               STR

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

Structure attributes must be viewed using STN Express query preparation.

L2               QUE   ABB=ON   PLU=ON   L1

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FILE 'REGISTRY' ENTERED AT 16:23:53 ON 05 FEB 2010

L1               STRUCTURE UPLOADED  
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L3               1 S L2  
L4               3 S L2 FUL

FILE 'CAPLUS' ENTERED AT 16:24:28 ON 05 FEB 2010

L5               3 S L4

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FULL ESTIMATED COST	17.93	209.69
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-2.55	-2.55

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